December 26, 2012

Documents Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

Re: Docket No. FDA-2012-P-1028
Comment and Request for Summary Denial of Petition

Dear Sir or Madam:

The undersigned pharmaceutical companies submit this Comment and Request for Summary Denial of Petition in response to the citizen petition filed by Reckitt Benckiser Pharmaceuticals Inc. ("RBP") dated September 25, 2012, identified as Docket No. FDA-2012-P-1028. The petition requests that the U.S. Food and Drug Administration ("FDA" or "the Agency") refuse to approve generic versions of RBP's flagship prescription drug products, Subutex® and Suboxone®. The undersigned companies are members of the Buprenorphine Products Manufacturers Group ("BPMG"), which was formed in early 2012 after the FDA directed all sponsors of pending and approved oral transmucosal buprenorphine-containing drug products for opioid dependency to enter into a single shared system ("SSS") Risk Evaluation and Mitigation Strategy ("REMS") under the Federal Food, Drug, and Cosmetic Act ("FD&C Act"). Rather than adhere to FDA's mandate and become a part of the industry-wide SSS REMS, RBP has chosen instead to file its citizen petition in an attempt to block competition for its buprenorphine drug franchise by raising baseless arguments under the pretext of patient safety. The undersigned companies state emphatically that patient safety is of paramount importance to them, and it will remain their highest priority with respect to generic buprenorphine-containing drug products. The petition is merely the latest salvo in RBP's 11-month campaign to obfuscate and delay FDA's approval process for generic buprenorphine-containing tablets. Because of this unlawful purpose, and because the petition contains inadequate legal or scientific support for its

requests, FDA should summarily deny RBP's petition, as contemplated by Section 505(q) of the FD&C Act.

I. Background

In order to fully understand how RBP's petition represents anticompetitive conduct, one must consider the facts underlying the marketplace for oral transmucosal buprenorphine-containing drug products for the treatment of opioid dependency.

The products at issue are single-ingredient Subutex (buprenorphine HCl) sublingual tablets and combination-ingredient Suboxone (buprenorphine HCl and naloxone HCl) sublingual tablets and sublingual film. The Subutex tablets have been subject to generic competition since the product's orphan drug exclusivity expired in 2009. The Suboxone tablets' exclusivity also expired in 2009, but the abbreviated new drug applications ("ANDA") for that drug are still pending before FDA. RBP's most recent addition to its buprenorphine franchise was approved by FDA in August 2010, as a sublingual film dosage form. Suboxone film is subject to a dosage form patent that will not expire until 2023. To our knowledge, no ANDAs have been filed with FDA that reference Suboxone film.

As a franchise, Suboxone is by far the most profitable of RBP's product lines, "with the pharmaceutical arm [of RBP] reporting operating margins of 68 per cent and accounting for roughly one-fifth of group operating profit last fiscal year."[1] In 2011, the franchise accounted for over $1.2 billion in sales.[2] Of these, prescription tracking data suggests that the sublingual film accounted for approximately 70% of $1.2 billion in sales, or $840,000,000.[3] More conservative estimates by RBP suggest that 60% of Suboxone revenues come from the film.[4] In fact, due to

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[1] A. Jack, L. Lucas, *Reckitt withdraws Suboxone over abuse*, Financial Times, Sept. 25, 2012, *available at* http://www.ft.com/intl/cms/s/0/fb04e75a-072d-11e2-b148-00144feabdc0.html#axzz2BYXNTBjm.

[2] J. Napodano, *Reckitt's Decision Opens The Door For Titan Pharma And BioDelivery Sciences*, Seeking Alpha, Sept. 26, 2012, *available at* http://seekingalpha.com/article/889861-reckitt-s-decision-opens-the-door-for-titan-pharma-and-biodelivery-sciences.

[3] *See id.*

[4] A. Jack, L. Lucas, *Reckitt withdraws Suboxone over abuse*, Financial Times, Sept. 25, 2012, *available at* http://www.ft.com/intl/cms/s/0/fb04e75a-072d-11e2-b148-00144feabdc0.html#axzz2BYXNTBjm*; see also* S. Thaxter, RBP CEO, *Building a sustainable growth business*, Reckitt Benckiser Pharmaceuticals Slide Presentation, July 2012, *available at* http://www.rb.com/DocumentDownload.axd?documentresourceid=29338.

RBP's concerted efforts to transfer patients from the tablet to the film, including giving rebates and coupons for the film but not for the tablet, the film's net revenue as a percentage of RBP's U.S. business increased from 40% to 60% between 2011 to 2012, whereas Suboxone tablet net revenue decreased from 60% in 2011 to 40% in 2012.[5]

The FDA approved RBP's REMS program for the Subutex tablets and Suboxone tablets on December 22, 2011. On or about January 6, 2012, FDA informed all pending and approved ANDA sponsors of oral transmucosal buprenorphine-containing products that these drug products would be subject to a SSS REMS. The FDA mandated a compliance date of May 6, 2012, by which time it expected all approved sponsors to join the SSS with RBP. Since January, the undersigned BPMG members have been attempting to work with RBP to develop a SSS REMS. Those efforts were unsuccessful due to RBP's obstructionist tactics, which have been detailed extensively in other Comments filed in response to RBP's petition,[6] and are also set forth in Addendum 1.

RBP's petition asks FDA to refrain from approving any applications for drug products containing buprenorphine for the treatment of opioid addiction, unless they comply with RBP's specified and patently baseless requests. In particular, RBP requests that FDA refrain from approving (1) any buprenorphine NDA or ANDA that does not include a targeted pediatric exposure education program, (2) any applications for buprenorphine that lack child-resistant unit-dose packaging, and (3) any buprenorphine/naloxone ANDA until FDA determines whether RBP discontinued Suboxone tablets for reasons of safety. None of these requests has merit.

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[5] S. Thaxter, RBP CEO, *Building a sustainable growth business*, Reckitt Benckiser Pharmaceuticals, July 2012, at Slides 5, 6, and 15, *available at* http://www.rb.com/DocumentDownload.axd?documentresourceid=29338.

[6] We reference the Comment filed by Venable LLP on October 22, 2012, on behalf of Amneal Pharmaceuticals, LLC, and the Comment filed by Actavis Inc. on November 28, 2012, available at Docket No. FDA-2012-P-1028.

II. Regulatory/Scientific Arguments

RBP's request that FDA make a determination whether Suboxone tablets have been discontinued for safety reasons raises several complex legal issues. The issues concern whether an FDA-approved product, that was previously considered safe, is rendered unsafe merely because the manufacturer claims that its second-generation product is safer due to a potential decrease in misuse by a population other than the intended user. The answer should clearly be no.

The Petition is Unlawful under Section 505(q) of the FD&C Act

In 2007, Congress stated in Section 914 of Title IX of the Food and Drug Administration Amendments Act ("FDAAA")[7] that FDA shall not delay approval of a pending ANDA or 505(b)(2) application as a result of a Citizen Petition or Petition for Stay of Action, unless FDA "determines, upon reviewing the petition, that a delay is necessary to protect the public health."[8] In so doing, Congress created Section 505(q) of the FD&C Act and gave FDA the express legal authority to deny a petition that is "submitted with the primary purpose of delaying the approval of an application" and that does not "on its face raise valid scientific or regulatory issues."[9] FDA has recognized that § 505(q) was intended to prevent the Citizen Petition process from being used as an anti-competitive tactic to delay approval of ANDAs and 505(b)(2) applications.[10] The petition at hand is just such a tactic that is intended to thwart generic competition. Because RBP's petition was submitted for an unlawful purpose, and is not scientifically justified, the petition should be summarily denied by FDA under § 505(q).[11]

A. Lack of Scientific or Regulatory Justification

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[7] Pub. L. No. 110-85 (2007), as amended by § 301 of Pub. L. No. 110-316 (2008), codified as 21 U.S.C. § 355(q).

[8] 21 U.S.C. § 355(q)(1)(A).

[9] 21 U.S.C. § 355(q)(1)(E).

[10] "Congress enacted this [505(q)] provision to *prevent* delays of ANDA approvals due to FDA's consideration of issues raised in citizen petitions." Fed. Def.'s Opp. to Pl.'s Mot. Prelim. Inj. at 25, *AstraZeneca Pharmaceuticals LP v. Food and Drug Administration, et al.*, 2012 U.S. Dist. LEXIS 54863 (D.D.C. 2012) (No. 12-cv-0338-CKK) (italics in original).

[11] For a detailed discussion on the applicability of § 505(q) to RBP's petition, please see Addendum 2.

FDA should deny RBP's petition because it does not raise valid scientific or regulatory issues. RBP's petition discusses almost exclusively its purported "safety concerns" regarding the labeling and packaging of buprenorphine-containing tablets.[12] Yet, as the NDA Sponsor for the "reference listed drugs" ("RLD"), RBP has control over the labeling and packaging aspects of Subutex and Suboxone and has sold the products for years with the exact labeling and packaging that the company now vilifies. Consequently, RBP is using safety as a pretext.

RBP spends the bulk of its time in the petition's analysis section discussing two criteria under which FDA should not approve pending buprenorphine applications: (1) if the pending applications does not include a targeted pediatric exposure education program; and (2) if the pending applications lack child-resistant unit-dose packaging.[13] Neither issue is supported by substantive, validated scientific evidence. Likewise, RBP's suggestion that the packaging of buprenorphine is one of the drug's main threats to pediatric safety is not supported by the Venebio study referenced by RBP or any scientific literature cited by RBP, as discussed herein. In fact, the Venebio study provided by RBP is not even complete; it is merely a summary report of a study which describes little credible scientific fact and offers no underlying data that can be analyzed by FDA or independent investigators. Given the significant deficiencies in the data and analysis presented by RBP, it is difficult to see how the FDA could rule that the petition has included substantive scientific evidence. In sum, RBP's reasoning as to why FDA should not approve a pending buprenorphine NDA or ANDA does not raise any valid scientific or regulatory issues. The quasi-scientific data presented in the petition are incomplete, superficial and not validated. Consequently, FDA should deny the petition.

1. **Response to RBP's Claim that a Targeted Pediatric Exposure Education <u>Program Is Necessary as part of an NDA and ANDA Approval</u>**

    a. There is Insufficient Information to Conclude on the <u>Influence of Education on Accidental Pediatric Exposures</u>

[12] *See supra* note 7.

[13] *Id.* at 29-42.

The impact of the pediatric education component conducted by RBP on the rate of unintentional pediatric exposures is not demonstrated by data submitted to the docket in support of RPB's petition or any other published validated scientific study. RBP purports to rely on the Executive Summary of the Venebio study, "Accidental Exposure to Buprenorphine in Children," without providing the report or the underlying data for public analysis.[14] It is stated in several instances that it is not possible to conclude on the influence of education on unintentional pediatric exposures.[15] The following quotations from that Executive Summary illustrate that point:

> "*Overall there was insufficient information in the case narratives from Poison Centers and the RBPPV database to determine whether physician/patient education influences the risk of unintentional pediatric exposure."*
>
> *"The Poison Center reports (representing >98% of cases analyzed herein) that we reviewed did not include information regarding physician/patient education."*
>
> *"While there was insufficient information available on the use of physician/patient education to make definitive conclusions regarding its influence, further analysis of the data is ongoing to understand the impact of packaging on unintentional pediatric exposures. "*

As the final results were not presented in the Executive Summary, a full analysis was not possible; however, one can reasonably conclude that there are no solid data to support the claim that pediatric exposure education is a definitive requirement for approval of buprenorphine/naloxone products. It is particularly striking that over 98% of the data that RBP references in the petition to

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[14] In RBP's recently filed comment [CITE], RBP cynically challenges Amneal Pharmaceuticals' characterization of the data and analysis based on the fact that Amneal has not seen the data and analysis. RBP Comment at 3. RBP further highlights its gamesmanship by complaining that Amneal refers to its data as a "safety signal" even though Amneal has not seen the data. *Id*. at 2. Of course, spontaneous reporting data can provide only a signal in the absence of further scientific verification. RBP accompanies its comment with a copy of a reported death associated with pediatric exposure. This report illustrates one of the fundamental problems with RBP's hidden data and analyses and, more fundamentally, with RBP's attempt to rely broadly in numbers of reports of pediatric exposure. The report does not state or imply that the exposure was related to the absence of an educational campaign or unit-dose packaging. It does not even state or imply that the exposure was accidental. The report and accompanying news story suggest instead that the exposure might have been a misguided attempt by a parent to medicate a restless child.

[15] Indeed, for RPB to claim a mitigating influence of education on unintended exposures, measurements of the incidence of unintended exposures would be required for time periods before and after education in populations that received education. At best, RBP has cited only the sporadic reporting of example cases of unintended exposure with conjecture and hypotheses but with no measurable risk reduction.

support its claim has no information regarding education at all, and is therefore of no value in supporting that claim.

The conclusions that are presented in the petition cannot be supported by the evidence as presented; therefore, these conclusions are premature and have limited scientific merit. These conclusions are drawn upon unsubstantiated conjecture and hypotheses that are not developed in an appropriate manner and they do not constitute sufficient evidence that pediatric exposure education would change the risk-benefit profile of buprenorphine products. Thus, pediatric exposure education should not be a requirement for approval of buprenorphine-containing products.

Companies with past experience in developing SSS REMS programs know that the elements of the REMS are determined throughout the development of both individual REMS programs and SSS REMS programs with the FDA. If important elements are identified by FDA, these will be included in the REMS to ensure the success of the program. It is inappropriate to negotiate the elements of a REMS program through a citizen petition.

b. Pediatric Risk is Already Communicated in the Currently-Proposed Labeling and REMS Program Under Review by the FDA

Pediatric exposure risk for buprenorphine products is not a new notion. This risk has been known since the approval of the drug in 2002 and is shared with all other opioids with much longer approval histories, as well as any potent medication on the market. In the currently approved labeling for Suboxone tablets,[16] pediatric risk is already mentioned multiple times very clearly:

a) In the "Highlights of Prescribing Information":

"Store SUBOXONE sublingual tablet safely out of the sight and reach of children. Buprenorphine can cause severe, possibly fatal, respiratory depression in children."

b) Under "5. Warnings and Precautions":

[16] Ref ID 3063079, Issued December 2011, Approved Dec. 22, 2011

"5.4 Unintentional Pediatric Exposure

Buprenorphine can cause severe, possibly fatal, respiratory depression in children who are accidentally exposed to it. Store buprenorphine-containing medications safely out of the sight and reach of children."

c) Under "16. How Supplied/Storage and Handling":

"Patients should be advised to store buprenorphine-containing medications safely and out of sight and reach of children. Destroy any unused medication appropriately."

d) Under "17. Patient Counseling Information":

"17.1 Safe Use

Patients should be instructed to keep SUBOXONE sublingual tablets in a secure place, out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Patients should be advised that if a child is exposed to SUBOXONE sublingual tablets, medical attention should be sought immediately."

e) In the "Medication Guide":

In a Boxed Warning:

"IMPORTANT:
Keep SUBOXONE in a secure place away from children. Accidental use by a child is a medical emergency and can result in death. If a child accidentally uses SUBOXONE, get emergency help right away."

"How should I store SUBOXONE?

Keep SUBOXONE in a safe place, out of the sight and reach of children.

[Bold font in original.]

Generic drugs have the statutory requirement to provide the same labeling as the RLD; therefore, pediatric risk will be similarly warned about multiple times in the labeling of the generic versions of buprenorphine/naloxone tablets. Moreover, warnings against pediatric exposure are also part of RBP's currently approved REMS. Likewise, the proposed REMS that has been submitted to the agency by the generic sponsors seeking approval for buprenorphine/naloxone tablets also incorporated numerous warnings against pediatric exposure in several documents, including the Dear Healthcare Professional Letters, the Physician Brochure, the Pharmacist Brochure, the Important Safety Information, and the Medication Guide. It is difficult to argue

against the fact that the risk of pediatric exposure is already clearly communicated in numerous instances in the product labeling and the REMS, and the same will apply to approved generic buprenorphine/naloxone tablets.

2. **Response to RBP's Claim that Child-Resistant Unit-Dose Packaging is Necessary as part of an NDA Approval**

a. Some Results from the Venebio Study may Present Substantial Biases

In the Venebio study Executive Summary, data are presented with very little effort to explain potential causes of bias. For example, potential bias in the results can be seen in the mean reporting rates of pediatric exposures by unique recipients of dispensed drug ("URDD"). It is not clear why risk standardized by URDD would be only 2.51 cases/10,000 URDD for buprenorphine single-ingredient tablets and 6.25/10,000 URDD for buprenorphine combination-ingredient tablets. It equals to a 2.5 fold risk-ratio between these two products even if they share the same form factor and the same packaging. No attempt is made in the Executive Summary to explain that difference. Actually this difference is not even pointed out. When such a difference in results exists between two products that share the same packaging, it is hard to believe that packaging is a sufficient explanation to the lower rate observed with the film formulation, and other confounding factors certainly exist and should have been explored.

Several gaps in the methodology employed by Venebio are easy to identify. For example, it does not seem that any provision was taken to account for repeated measurements from the same poison centers over time, producing random duplicates of cases. As another example, missing data are not presented on buprenorphine-containing products where no specific formulation was identified, as would be required in any credible scientific publication, calling into question the judgment of relying on this single study to arrive at the conclusions in the citizen petition.

Further, there may be fundamental differences between the patient who receives buprenorphine combination tablets versus film that make a direct comparison between them invalid. Regardless of URDD-adjusted volume, the analysis presented in the petition inherently makes the assumption that patients are equally likely to have received any one of the three

formulations since no attempt was made to correct for selection bias by treatment allocation. In effect, the analysis assumes that U.S. treatment programs were engaged in a randomized trial of the three buprenorphine formulations, and that clinicians assigning patients to therapy were completely unaware of potential pediatric exposure benefits of one formulation over another. This is simply impossible to believe. If, for example, the single ingredient tablet was dispensed preferentially to women (i.e., under the belief that it is safer during pregnancy than the combination product), there is the possibility that children would have been more likely to be in a physical place with the single ingredient product than other formulations given the societal expectations of caregiving in this demographic group. The observed differences between the formulations could just as well be explained as a function of differences in the underlying population receiving the drug, and independent of any impact of packaging. The onus is on RBP to provide the scientific justification for why it is appropriate to ignore selection bias in this analysis, and provide the evidence showing that patient allocation between the products was comparable with respect to potential pediatric exposure risk.

For all of these reasons, the results of the Venebio study should be interpreted with caution.

b. The Nature of the Packaging is only One of Many Factors to Consider when Looking at Pediatric Drug Exposures

Unit-dose packaging may simply not be as efficient in reducing pediatric exposure as it may seem. Referring to the Venebio study Executive Summary, under "On the potential role of product packaging", one can only interpret this data with limited understanding as few details are provided. The data gives the impression that 90.5% of the film cases and 85.2% of the combination-ingredient tablets cases provide no information regarding how the product was packaged. It is unclear if the data is unknown, not provided, or simply not available and no effort is made to clarify the methodology that was used to collect and assess this data. As presented, the only limited conclusion that can be derived from this data is that, in a very large majority of the cases of pediatric exposure, the drug product may or may not have been enclosed in the child resistant packaging when the child gained access to it. The results presented in the Venobio study Executive Summary are too incomplete to lead to any conclusion about the influence of packaging

on the risk of pediatric exposure; therefore, do not support RBPs conclusions. It is quite possible that the packaging only had a marginal difference in the risk of pediatric exposure and proper handling by the patient is potentially far more efficient at reducing that risk.

Actually, the FDA itself did not agree that the packaging of Suboxone film provides a meaningful incremental protection against pediatric exposure and stated that a third party is likely to remove the drug product from the packaging:

Question 4:

a) Does FDA agree that the packaging for SUBOXONE Sublingual Film provides meaningful incremental protection against pediatric exposure?

FDA Response:

No, we do not agree that the packaging for buprenorphine HCl and naloxone HCl sublingual film provides meaningful incremental protection against pediatric exposure. Although the foil pouches fulfill the child resistant effectiveness standards and the foil pouch bears warning statements alerting patients to keep out of reach of children, no data were provided to support that these measures will encourage patients to store buprenorphine HCl and naloxone HCl sublingual film in a manner which prevents accidental pediatric ingestion. Because patients are known to divide tablets, it may be expected that patients will remove films from the package and have partial doses that are neither in the child-resistant pouch nor in a child-resistant medication bottle. Furthermore, because the film cannot be spit out (unlike a tablet) it is possible that a child who obtains access to even one dose might be more adversely affected than a child who obtains access to a single tablet.[17]

Moreover, attributing the risk of pediatric exposure solely to the nature of the packaging is over-simplifying a complex situation and under-estimating the influence of the drug product itself. One of the possible explanations to the fact that pediatric exposures to the tablet formulation are more numerous than for the film formulation may be found in the simple fact that tablets are possibly more appealing to children. This simple fact has the potential to introduce a sizeable bias in the risk of pediatric exposure which is not related to the nature of the packaging per-se. Just as a ban on all tablet form drugs would be an unreasonable response to the Venebio study, so is a blanket requirement for unit-dose packaging.

[17] Suboxone sublingual film, ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS, page 27, http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022410Orig1s000AdminCorres.pdf.

Finally, ignoring the potential biases, the petition seems to largely attribute the risk of pediatric exposure to the nature of the packaging used, while the Executive Summary of the Venebio study which RBP chose as a basis to demonstrate causality does not provide any precise conclusion about that point and prudently states that further analysis of the data and expert review is needed:

"While there was insufficient information available on the use of physician/patient education to make definitive conclusions regarding its influence, further analysis of the data is ongoing to understand the impact of packaging on unintentional pediatric exposures."

RBP evidently chose to extrapolate the results of this study and draw its own conclusions beyond the conclusion of the authors of the study. For this very reason, the scientific value of RBP's conclusions about the influence of packaging is open to debate and is insufficient to support the request that FDA force sponsors for buprenorphine containing products to use child-resistant unit-dose packaging.

c. RBP Could Have Used Unit-Dose Packaging for Suboxone Tablets But Chose Not to Pursue that Option

The most compelling retort to RBP's petition is the company's own evident hypocrisy. If there was such an urgent need for a unit-dose packaging of buprenorphine combination-ingredient tablets, it is hard to understand why RBP did not choose to implement unit-dose packaging for Suboxone tablets to address the safety concern of pediatric exposure in the U.S., but instead chose to wait several years without addressing that point and then suddenly announce the discontinuation of the drug for safety reasons. Suboxone has been distributed in numerous countries around the world in unit-dose packaging for many years. In continental Europe, unit-dose blister packages have been available since the introduction of the product (approved by the European Medicines Agency in October 2006) and a unit-dose blister packed form of Suboxone is available in Canada (approval in May 2007).

Given these facts, it is hard to understand why RBP chose not to introduce unit-dose packaging for Suboxone tablets in the U.S., especially if the signals for risk of pediatric exposure were so concerning to them. It is hard to believe that there are any significant technological or regulatory barriers to unit-dose packaging in the U.S. when this drug is being successfully blister-

packed in Canada and Europe. In the petition, RBP concedes that unit dose packaging would be feasible; however, instead of addressing this important issue, they continued to sell the multiple-pill bottles and chose to focus resources on the development of the Suboxone film dosage form. Clearly this decision was market driven given that the Suboxone tablets were nearing market exclusivity expiration and this product was no longer considered a priority, even from a patient safety and pediatric risk perspective.

In sum, there is no scientific justification for RBP's decision to refuse to repackage its Suboxone tablets into a child-resistant unit-dose form and, instead, to withdraw the product from the market. The only logical inference is an anti-competitive one.

d. Unintentional Pediatric Exposure Is Not Specific to Buprenorphine

While we understand that pediatric safety is an important concern, there is little, if any, scientific support for a decision to focus on buprenorphine, of all opioid drugs and other drugs of different classes presenting a risk for pediatric exposure, and declare that unit-dose packaging is a regulatory requirement. The problem of unintentional pediatric exposure, and whether unit-dose packaging is the solution for it, would be better approached from a systemic point of view, looking at the entire spectrum of products in the pharmaceutical industry, as well as the entire supply chain, and various packaging configurations, and not focusing on buprenorphine which is not the most harmful product for unintentional pediatric exposures. The same is inherently true for the pediatric education component of the petition which does not apply to buprenorphine alone, or even to opioids as a class, but arguably to all potent drugs on the market.

It is important to note that several other drugs present a risk profile comparable or worse than opioids in terms of a safety hazard to children in cases of unintentional exposure. Several other classes of drugs available in solid oral forms show a significant risk in cases of pediatric exposure to even one pill. Such drugs include, for example, calcium channel antagonists, clonidine and other imidazolines, cyclic antidepressants, diphenoxylate/atropine, salicylates, and sulfonylureas, all of which have the potential to cause adverse effects that are more severe than buprenorphine and for some of which no antidotes are available. Although these drugs, as well as opioids, present a significant and potentially life-threatening health risks with pediatric overdose,

the FDA has not deemed it necessary to place them in unit-dose or other child-deterrent packaging beyond child-resistant bottles.

A citizen petition focusing on one specific drug product is not the appropriate vehicle for FDA's consideration of how packaging types might affect drug safety and accidental pediatric exposures as a whole.

3. **Response to RBP's Claim that Suboxone Tablets Were Withdrawn from the Market for Reasons of Safety**

a. The Perceived Safety Signals Identified in the Venebio Study Are Not Reproduced in FDA's Adverse Event Databases

While RBP's petition cites a dramatic increase in reports of accidental pediatric exposures for buprenorphine-containing products, RBP's assertion of increased risk to public health has not been captured in FDA's adverse event reporting databases. A review of the publicly available quarterly reports of "Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System," issued for medications with increased events posing a public threat, does not reveal any indication that either Suboxone or Subutex have ever been flagged as threats. These reports, available on the FDA website, extend from 2008 to 2012, which would include the time period reviewed in the Venebio study, which are cited as the most dangerous for the accidental pediatric exposures. The increase in reported pediatric exposures, in and of itself and in consideration with reported safety outcomes, did not elicit a new safety signal by either RBP or the FDA's own monitoring system.

b. RBP Failed to Develop a Timely Response to Perceived Safety Signals

RBP points out that its RiskMAP was approved in conjunction with the approval of Subutex and Suboxone in October 2002. As part of this RiskMAP, RBP claims that it undertook "an expansive monitoring and reporting initiative."[18] RBP later admits to an "adjusted and improved" RiskMAP to address the emergence of pediatric safety concerns stemming from an unanticipated spike in pediatric exposures to buprenorphine, including "targeted educational interventions."[19] Even though RBP states in its petition that a significant trend regarding reported

[18] *See supra* note 7.

[19] *Id.*

pediatric exposures emerged in 2006-2007 (and indeed references a citation as far back as 2004), and further notes that the number of reported unintentional exposures was increasing at a rate higher than expected in 2009,[20] the Executive Summary of the Venebio study was not prepared until September 2012. It appears that, rather than quickly and definitively addressing these potential safety concerns when initially reported prior to 2009, as it now suggests is necessary, RBP noted in its discussion of reports of unintentional pediatric exposures to buprenorphine and other opioids in 2009 that "findings have stimulated further product research and development at RBP."[21] The timing and substance of RBP's latest actions seem more directed to address the specter of generic competition instead of a concerted, focused response to perceived safety signals noted by RBP as early as 2006. Overall, pediatric exposure risks suggested by RBP, if valid, might have resulted, in part, from its own ineffective and delayed reaction. This point should be considered when the FDA determines whether Suboxone tablets were discontinued for reason of safety (once they are, in fact, discontinued).

Finally, generic buprenorphine products potentially employ improved measures to address pediatric exposures that will result in a safety profile superior to that of Suboxone. For example, close collaboration with the FDA on an improved SSS REMS program that addresses the safety concerns the FDA may express has the potential to improve the overall safety profile of generic buprenorphine-containing tablet products, making it superior to the overall safety profile of the currently-packaged Suboxone tablets.

c. Suboxone Tablets Were Discontinued Primarily for Marketing and Strategic Regulatory Reasons

According to RBP's petition, pediatric exposures to both buprenorphine and buprenorphine/naloxone products have been reported for several years, with such reports reaching a peak in 2010. RBP thus concludes that there was ample time to consider discontinuation of the product if the company believed there was a safety concern, especially after the launch of the film formulation of the combination drug. Rather than discontinuing its tablet formulation, RBP strategically chose to announce discontinuation of its product shortly before generic competition is expected to enter the market. It is no coincidence that RBP has been trying to aggressively push

[20] Cynthia G. McCormick, et al., *Case histories in pharmaceutical risk management*, 105 S(Suppl. 1) Drug and Alcohol Dependence S52 (2009).
[21] *Id.*

for the use of the film to patients, prescribers, insurers, and Medicaid agencies for more than a year, well before the time of their sudden alleged "discovery" of the risk of perceived pediatric exposure risk to the tablets. Also, it is unclear when this discontinuation will actually take place as no firm date has been announced and the distribution of Suboxone tablets continues. If the safety concern from RBP was as important as they attempt to depict, one would expect a clearer plan concerning discontinuation, and possibly a communication plan to affected stakeholders, or even a recall of the tablets on the market, rather than an announcement via citizen petition and a request that FDA refuse to approve generic drugs.

All these elements make it clear that RBP is discontinuing Suboxone tablets for marketing and strategic regulatory reasons and not for safety reasons.

d. The Overall Safety Profile of Suboxone Film is Not Fully Characterized

Although the citizen petition is focused on pediatric exposures to buprenorphine tablets, it is important to point out that the film products have become a significant concern to law enforcement, specifically in prisons. Because the film strips are flat, they are easily placed under stamps, in bindings of books and hems of clothing and are smuggled into jails and prisons. In order to do this, the strips have to be removed from packaging and thus would be loose and available for easy access by young children. For instance:

> *According to HCDC (Harlan County Detention Center) officials, Suboxone strips are one of the biggest problems they face as far as drugs being sent into the jail. As early as 2011, word spread about Suboxone strips and how easily they could be smuggled into a detention facility. The problem became so widespread many facilities have begun removing mail all together and replacing it with post cards sold at the jail commissary.*
>
> *White T-shirts, socks and underwear supplied to inmates from family and friends were also being utilized as a means of getting the strips past authorities to inmates. The strips are easily hidden behind false tags or sewed into the seams of a garment.*[22]

[22] J. Asher, "Four charged in jail contraband investigation," The Harlan Daily Enterprise, McClatchy-Tribune Information Services, Harlan, Ky, October 13, 2012, *available at* http://www.harlandaily.com/view/full_story/20480882/article-Four-charged-in-jail-contraband-investigation.

The observed phenomenon is related to the form factor of the film that makes it easier to conceal and smuggle. The same concerns may as well be applicable to the entire adult population of buprenorphine products, particularly dealers and misusers/abusers. Therefore, when viewed in totality, it seems that Suboxone film does not have a better overall safety profile than the tablet, especially when factoring in the specific detention facility population.

e. When Unintentional Pediatric Exposure Does Occur, a Unit of the Film Product is Potentially More Dangerous than a Unit of the Tablet Product

Because buprenorphine has better oral transmucosal absorption than in the gastro-intestinal tract following which there is significant first pass metabolism effect, the potential severity of pediatric exposure to the film is greater than the potential severity of pediatric exposure to the tablet, which will more likely be swallowed or chewed and rapidly swallowed rather than be kept in the mouth for transmucosal absorption. Under normal conditions of use, the complete dissolution of the tablets takes 7 to 12.4 minutes.[23] It is unlikely that a young child exposed to the tablet will keep the tablet in the mouth for such a period of time before swallowing it or spitting it out because of the bitter taste, and even more unlikely that it will be kept under the tongue. It is actually a common situation to retrieve sizeable fragments of tablets from the gastric lavage cases of pediatric unintentional exposures which shows that chewing before swallowing was minimal. It can be hypothesized that the most likely situation if exposure occurs is that the tablet will be rapidly entering the stomach in its whole form or coarsely fractioned after partial chewing. In that context, systemic exposure to buprenorphine will be limited to only a fraction of the actual dose absorbed during normal use because the bioavailability of buprenorphine in the gastro-intestinal tract is limited to about 10%.[24]

In contrast, in the case of exposure to the film formulation, there is less probability that the film will be swallowed whole as compared to the tablet because of the chances of adherence to the mucosa, the small and flat form of the product that decreases sensitive feedback of a foreign body

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[23] *See* http://www.suboxone.com,Why Suboxone film?, Dissolve time (last accessed Nov. 15, 2012).

[24] Welsh C, Valadez-Meltzer A. Buprenorphine: a (relatively) new treatment for opioid dependence. Psychiatry (Edgmont). 2005 Dec;2(12):29-39. PubMed PMID:21124750; PubMed Central PMCID: PMC2994593.

in the mouth cavity, the improved taste over the tablet,[25] and the natural physiological difficulty of swallowing very small objects. In particular, the highly hygroscopic characteristic and small and flat form factor of the formulation makes it likely to adhere to the mucosa of the mouth and stay there until complete dissolution, which is reportedly faster than for the tablet, between 5 and 6.6 minutes.[26] Considering these factors, pediatric exposure to the film has the potential to result in a systemic exposure comparable to the exposure possible during normal use, which ranges from 30 to 50%,[27] and possibly results in greater severity of adverse events. The fact that RBP recently added a new film strength containing 12 mg of buprenorphine, whereas the maximum dose present in a tablet is 8 mg, makes the risk for potentially harmful systemic exposure from the film even greater. There are actually no data in the citizen petition comparing the *severity* of adverse events encountered in pediatric exposures to the tablet compared to the film. The FDA itself pointed to that problem, specific to the film formulation:

Furthermore, because the film cannot be spit out (unlike a tablet) it is possible that a child who obtains access to even one dose might be more adversely affected than a child who obtains access to a single tablet.[28]

The arguments exposed above may lead to the conclusion that, in the case of exposure to a single dosage unit of the drug, the film may result in a greater systemic exposure than the tablet.

In sum, there is no regulatory validity or scientific merit to RBP's petition request.

III. **Legal Argument**

A. FDA Should Summarily Deny RBP's Petition Pursuant to § 505(q)(1)(E)

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[25] *See* http://www.suboxone.com,Why Suboxone film?, "Taste: In a patient questionnaire, more than 71% of patients who have tried SUBOXONE Film rated the taste as neutral or better on a 10-point scale" (last accessed Nov. 15, 2012).

[26] Suboxone sublingual film, ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS, page 27, http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022410Orig1s000AdminCorres.pdf.

[27] Welsh C, Valadez-Meltzer A. Buprenorphine: a (relatively) new treatment for opioid dependence. Psychiatry (Edgmont). 2005 Dec;2(12):29-39. PubMed PMID:21124750; PubMed Central PMCID: PMC2994593.

[28] Suboxone sublingual film, ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS, page 27, http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022410Orig1s000AdminCorres.pdf.

1. RBP's Primary Purpose in Submitting the Petition is to Delay the Approval of Generic Drugs

FDA should summarily deny RBP's citizen petition because RBP's primary purpose in submitting it to FDA is to delay approval of the pending buprenorphine/naloxone ANDAs (*i.e.*, delaying approval of generic competitor drugs). FDA is specifically authorized by § 505(q) to dismiss any petition that is submitted with the primary purpose of delaying approval of a pending ANDA.[29] In the case at hand, RBP is upfront about its intentions – the petition specifically asks FDA to refrain from approving ANDAs for buprenorphine-containing drugs. Without those approvals, RBP continues as the only U.S. marketer of buprenorphine/naloxone tablets. Knowing that FDA would need time to review, analyze and answer the petition, RBP ensured – by the mere submission of the document to FDA – that it would cause a delay in FDA's processing of the pending ANDAs. That delay, in turn, would foreclose market entry by generic competitors, with the effect of improperly extending RBP's monopoly and keeping its brand drug prices at supra-competitive levels.

Furthermore, the timing of RBP's petition is highly suspicious, as it very closely aligns with the BPMG's submission to FDA of an industry-wide SSS REMS that would bring the ANDAs even closer to final FDA approval. RBP had direct knowledge of the BPMG's plans for submitting the SSS REMS to FDA because RBP was a voting member of the SSS development group at the time and was privy to the BPMG planning and scheduling discussions. RBP worked disingenuously with FDA and the BPMG on the development of the SSS REMS, presenting misleading statements and half-truths, inordinately prolonging the SSS development process with irrelevant issues and scheduling glitches, and then ultimately refusing to sign on to the Memorandum of Understanding ("MOU").

RBP's petition is driven solely by a desire to delay and/or block generic competition. This desire for monopolistic control of the buprenorphine market is further evidenced by RBP's recent

[29] 21 U.S.C. § 355(q)(1)(E). Congress used the term "primary purpose" to signal that petitions could be filed for multiple purposes, and only one of those might cause a 505(q) prohibition. Therefore, even if the packaging issues raised by RBP are, at an academic level, worth FDA's long-term consideration, the issue does not change the primary purpose of the petition, which is a request that FDA refuse to approve generic drugs.

price increases for Suboxone tablets, while leaving the Suboxone film prices steady,[30] and RBP's efforts to transition patients to its patent-protected film product.[31] As such, the petition is unlawful under the FD&C Act and should be summarily denied by FDA.[32]

a. ANDAs Are Pending that Should Be Approved despite the Petition

RBP's anticompetitive tactics, including, but not limited to, its filing of a citizen petition, have delayed approval of certain pending ANDAs for oral transmucosal buprenorphine-containing products for opioid dependency by at least nine months. This delay has caused an additional cost to the U.S. healthcare system of approximately $260,000,000[33] and to the U.S. Government of approximately $52,000,000.[34] As described in the Background section above, the generic members of the BPMG have been attempting to complete an SSS REMS since January 2012. Furthermore, based on regulatory filings with FDA, certain BPMG members understand that their ANDAs would be approved but for the outstanding REMS issue. The RBP petition further confounds the FDA's approval timeline for these ANDAs. Even if FDA denies the petition, its existence could delay the approval of the pending ANDAs for buprenorphine/naloxone tablets because FDA's staff and resources are limited, and the Agency has admitted in the past that its ability to review ANDAs is impacted by its need to evaluate and respond to related citizen petitions.[35]

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[30] E. Silverman, "Reckitt's Suboxone Strategy Is Really About Patients or Profits?," *Forbes* (Oct. 12, 2012), *available at* http://www.forbes.com/sites/edsilverman/2012/10/12/reckitts-suboxone-strategy-is-really-about-patients-or-profits.

[31] S. Thaxter, RBP CEO, *Building a sustainable growth business*, Reckitt Benckiser Pharmaceuticals Slide Presentation, July 2012, *available at* http://www.rb.com/DocumentDownload.axd?documentresourceid=29338.

[32] We also assert that RBP's anticompetitive actions violate antitrust laws, see Addendum 3.

[33] Calculation based upon IMS data for sales of Suboxone® tablets and assumptions based on historical market patterns of generic conversion and price erosion resulting from generic competition.

[34] Based upon Wolters Kluwer data reflecting 20% of Suboxone ® for Federal/State Medicare/Medicaid.

[35] *In re Prograf Antitrust Litig.*, No. 1:11-md-2242-RWZ, 2012 U.S. Dist. LEXIS 12053, at *10; 2012-1 Trade Cas. (CCH) P77,809 (D. Mass. Feb. 1, 2012) ("In its opposition FDA pointed out that 'Sandoz's [ANDA].was pending for over [2 and ½ years. At least part of this period was directly attributable to the need to evaluate and respond to [Astellas' citizen petition.'") (parentheticals in original).

2. Even if FDA Does Not Summarily Deny the Petition, FDA's Delay of the Approval of Pending ANDAs is Not Necessary to Protect the Public Health

Under Section 505(q), FDA shall not delay approval of an ANDA because of a pending petition unless the Agency determines that a delay is necessary to protect the public health. There is no such public health risk here. RBP has sold Suboxone tablets in the U.S. since 2002 without using unit-dose packaging. Curiously, RBP has sold its buprenorphine line of products in unit-dose packaging in international markets for years.[36] If RBP is as concerned as it claimed to be in its petition about accidental buprenorphine poisoning, it stands to reason that RBP would have introduced unit-dose packaging in the United States years ago, at the same time it introduced such packaging in international markets. Thus, RBP's argument is a sham and not an imminent public health issue. If FDA does not summarily deny the RBP petition, the Agency can still process the pending ANDAs through to final approvals because the public health will not be negatively affected to any extent beyond the public health impact that has existed for the past 10 years, during which time RBP has marketed Suboxone in tablet form without unit-dose packaging. FDA's decision to approve Suboxone tablets in multiple-pill bottles was based on a reasonable risk-benefit analysis, and that analysis should be employed for the pending ANDAs at the present time.

3. RBP's Petition Should Be Denied Because its Certification Statement Contains a Material Misrepresentation

Section 505(q)(1)(H) requires each petitioner to sign a certification statement attesting to the accuracy of the information in the petition. Specifically, the petitioner must certify as to the date that the information became known to the petitioner. The petitioner also must certify that the petition includes representative data and/or information known to the petitioner which are unfavorable to the petition. RBP's petition contains a certification statement, but the certification contains a material misrepresentation and is therefore deficient. Thus, the citizen petition should be summarily denied.

RBP stated in the petition certification that "the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted

[36] E. Silverman, "Reckitt's Suboxone Strategy Is Really About Patients or Profits?," *Forbes* (Oct. 12, 2012), *available at* http://www.forbes.com/sites/edsilverman/2012/10/12/reckitts-suboxone-strategy-is-really-about-patients-or-profits.

on or about the following date: September 15, 2012."[37] RBP's stated justification for requesting that FDA refrain from approving any buprenorphine NDA or ANDA for opioid dependence treatment is its purported concern with accidental buprenorphine poisonings. But RBP knew about the potential for accidental poisonings well before September 15, 2012. In fact, RBP has been looking into the issue of unintended pediatric exposures for quite some time.[38] However, RBP did not view the accidental poisonings as a "safety" issue during the time that it was reaping monopoly profits from Suboxone tablets.

RBP also failed to mention its concerns to the BPMG, despite engaging in six months' worth of discussions about the development of an SSS REMS. The REMS details how health care practitioners and pharmacists would be educated on safe practices for prescribing, dispensing and administering the drug (*e.g.*, Dear Healthcare Professional Letters, the Physician Brochure, the Pharmacist Brochure, the Important Safety Information, and the Medication Guide), and despite simultaneously presenting the pediatric exposure information to investors.[39]

RBP's intentional use of incomplete and misleading information, and its concealment of the information until its maximum anti-competitive impact could be felt, is sufficient grounds for FDA's denial of the citizen petition based on a deficient certification statement. Even if FDA does not summarily deny RBP's petition pursuant to section 505(q)(1)(E), the Agency should deny the petition because its certification statement contains a material misrepresentation.

B. Suboxone Tablets have not been Withdrawn from the Market for Safety Reasons

In conjunction with filing the petition, RBP informed FDA and the public that it intends to stop marketing Suboxone tablets within the next six months, and will move all of its sales and marketing efforts to its sublingual film product.[40] The timing of RBP's withdrawal is questionable

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[37] *See supra* note 7, at 48.

[38] RBP stated "… an alarming trend regarding pediatric safety emerged in 2006-2007," *supra* note 17, at 2.

[39] S. Thaxter, RBP CEO, *Building a sustainable growth business*, Reckitt Benckiser Pharmaceuticals Slide Presentation, July 2012, at Slide 12, *available at* http://www.rb.com/DocumentDownload.axd?documentresourceid=29338

[40] "Reckitt's decision to remove Suboxone® tablets from the market puts almost $400 million in sales up in play. Reckitt is clearly hoping to convert that $400 million over to its sublingual film formulation." J. Napodano, "Reckitt's Decision Opens The Door For Titan Pharma And BioDelivery Sciences," Seeking Alpha, Sept. 26, 2012, *available at* http://seekingalpha.com/article/889861-reckitt-s-decision-opens-the-door-for-titan-pharma-and-biodelivery-sciences.

and unconfirmed. The product has not been withdrawn to date, and even if it is withdrawn in the future, the reason for the withdrawal is commercial, and not safety-related.

1. Presently, Suboxone Tablets Are Not Withdrawn from the Market

Despite its statement, RBP has not stopped selling Suboxone tablets. The tablets are still available for sale at retail pharmacies, and via Internet sales. RBP's website still contains a "Dear Patient" letter stating that the tablets will be discontinued "within the next six months."[41] The product is also listed in the "active" Rx section of FDA's Orange Book.[42] While RBP's recent comments to the petition docket cite section 506C of the FD&C Act,[43] its public statements are inconsistent with the requirements of the statute. If RBP was complying, it would be required to wait six whole months before effectuating the discontinuance, not some undetermined period up to six months.[44] But more importantly, if the safety concern is as severe as RBP maintains, there is no reason RBP or FDA would permit such a "dangerous" product to remain on the market for any period of time. RBP knows, however, that the announcement of its product withdrawal is important because generic versions of a drug cannot be approved by FDA if that drug (the RLD) has been withdrawn from the market for reasons of safety or efficacy. 21 C.F.R. §§ 314.161(a), 314.127(a)(11). In the case at hand, because the tablets have not been voluntarily withdrawn by RBP, FDA may approve pending ANDAs that use Suboxone tablets as the RLD.

2. The Future Withdrawal of Suboxone Tablets is Irrelevant to FDA's Present Approval Decision for Pending ANDAs

If RBP's true intent is to withdraw the product in the future, that future withdrawal should not have any effect on the pending ANDAs that reference Suboxone tablets. FDA does not have the authority to hold or delay the approval of an ANDA due to a company's consideration of

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[41] *See* http://www.suboxone.com/?gclid=CKWB8P2_0bMCFY-d4AodxiMA5g, "For patients taking the tablet form of Suboxone® (buprenorphine and naloxone), Important Medication Update," which links to a "Dear Patient" letter, *last accessed* Nov. 15, 2012.

[42] *See* FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, 32nd ed. (last updated: 10/16/2012), *available at* http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm, *last accessed on* Nov. 15, 2012.

[43] Reckitt Benckiser Pharmaceuticals Inc., Comments to Docket No. FDA-2012-P-1028 (Nov. 16, 2012).

[44] "A notice required under subsection (a) shall be submitted to [FDA] at least 6 months prior to the date of discontinuance or interruption." 21 U.S.C. 356c(b)(1), as amended by Pub. L. No. 112-144 § 1001, 126 Stat 993, 1099 (2012).

withdrawing the RLD in the future. FDA has previously considered a similar untimely-filed petition – that is, before the product was actually withdrawn – but the Agency did not answer until the company provided a date certain on which it stopped distribution. *See* FDA Response to Citizen Petition, FDA Letter to ISTA Pharmaceuticals and Covington & Burling, FDA Docket Nos. FDA-2008-P-0368 and FDA-2011-P-0128 (May 11, 2011).[45] Therefore, RBP's future actions are irrelevant at the present time, and FDA has the legal authority to continue processing pending ANDAs through to final approval.

3. RBP has Significant Commercial Reasons for Announcing a Future Withdrawal of Suboxone Tablets

RBP's recent claim that it is withdrawing Suboxone tablets from the market is specious and, at best, misleading. While RBP claims that it is withdrawing Suboxone for safety reasons, RBP has publicly stated that it will continue to market Suboxone in a sublingual film dosage form. If Suboxone were unsafe, RBP would pull the product completely off the market. Instead, RBP has confirmed that Suboxone is safe. The only question involves the tablet dosage form's packaging configuration and not the product itself. Importantly the packaging issue is merely a diversion to remove attention from its fundamentally anti-competitive intent..

FDA is lawfully permitted to consider unstated but likely business reasons when it judges RBP's claims of a future product withdrawal. In the applicable regulation preamble, FDA has explained that, "The agency may determine whether a listed drug was withdrawn from sale for safety or effectiveness reasons . . . by attempting to focus on the intent of its manufacturer." 54 Fed. Reg. 28872, 28907 (July 10, 1989). In so doing, FDA may rely on direct evidence, circumstantial evidence, and logical inference to determine a manufacturer's actual intent. *Id.* FDA also may rely on information from third parties, including an ANDA sponsor. *Id.* at 28905. These other types of evidence are important, since the drug's manufacturer often has commercial reasons for making its "regulatory" decisions. While we acknowledge RBP's claim in its recent comments to the docket that ANDA applicants themselves have commercial reasons for opposing

[45] At pages 1 (footnote 1), 2 and 15. FDA explained that ISTA initially submitted a petition in 2010 before it stopped shipping the "withdrawn" product, but then withdrew that petition and submitted another petition in 2011. ISTA announced its intention to discontinue Xibrom in early 2011, ceased shipping as of February 28, 2011, and filed the second petition on March 1, 2011, asserting that Xibrom was withdrawn from the market for safety reasons. FDA denied the second ISTA petition on May 11, 2011.

the citizen petition, we point out that this fact is irrelevant, since the generic interests are clearly aligned with the Hatch-Waxman Amendments to the FD&C Act, while RBP's actions to unlawfully extend its monopoly past its patent term are fundamentally in opposition to it. FDA is well aware of the pharmaceutical industry's "life-cycle management" efforts, and the circumstance where a first generation drug is withdrawn from sale for the purpose of converting prescriptions to a second generation drug. The Agency is not required to take the withdrawing company's claims at face value. *See .e.g.*, 57 Fed. Reg. 17950, 17971 (Apr. 29, 1992) (FDA "would not consider the NDA holder's stated reasons for withdrawing a drug to be determinative because such remarks could be biased"); FDA Response to Citizen Petition, Letter to Leydig, Voit & Mayer and Covington & Burling, FDA Docket Nos. FDA-2011-P-0339 and FDA-2012-P-0507 (Nov. 7, 2012) (FDA denied drug manufacturer's petition claiming first-generation drug was withdrawn for safety, and replaced with second-generation drug).

In this case, although RBP claims that its concern for "pediatric exposure" is the reason it will withdraw the product in the future, life-cycle management and its bottom-line are the real reasons. Industry-watchers have stated as much,[46] noting that the timing is highly suspect given the imminent market entry of generics.[47] RBP stands to lose up to $400 million in sales and 20% of its gross profit if generic products compete with the Suboxone franchise. RBP has admitted that generic tablets will even take back some of the prescriptions that were already converted to

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[46] J. Napodano, "Reckitt's Decision Opens The Door For Titan Pharma And BioDelivery Sciences," Seeking Alpha, Sept. 26, 2012 ("we see a clear ulterior motive to the decision. Suboxone® tablets lost patent protection in 2009. As of yet, generic competition from alternative buprenorphine and naloxone tablets is non-existent. However, Reckitt's goal is clearly to transition patients over to the still on-patent sublingual film. In fact, Reckitt has filed a Citizen's Petition asking the U.S. FDA to require all manufacturers of buprenorphine products implement public health safeguards around pediatric exposure through educational campaigns and child resistant packaging. Suboxone® tablets were previously sold in a bottle containing 30 pills. So while Reckitt may take a short-term hit to its top line by removing Suboxone® tablets from the market, in the long run the company benefits from seeing less generic competition and more (forced) migration over to its under-the-tongue film."), *available at* http://seekingalpha.com/article/889861-reckitt-s-decision-opens-the-door-for-titan-pharma-and-biodelivery-sciences.

[47] *See* A. Jack, L. Lucas, "Reckitt withdraws Suboxone® over abuse," Financial Times, Sept. 25, 2012, ([RBP was "citing a US Poison Control Center study that there was eight times a greater risk of accidental unsupervised exposure by young children to the tablets in a bottle than the tamper-proof film. However, a presentation it gave in July showed there were very few cases: six exposures to the under sixes per million units dispensed."), *available at* http://www.ft.com/intl/cms/s/0/fb04e75a-072d-11e2-b148-00144feabdc0.html#axzz27hNXkQqw.

the film product.[48] Accordingly, "RBP has been encouraging the use of its film version, which melts on the tongue, as it fears the entry of generic competition to its tablets."[49]

4. RBP's Reason for Announcing a Future Withdrawal of Suboxone Tablets Is Not Safety-Related

Furthermore, even if RBP moves completely to the film dosage form in the future, the change does not mean that the tablet dosage form is not safe. In fact, FDA has recently looked at this very issue. Specifically, FDA denied a citizen petition filed by ISTA Pharmaceuticals, Inc., in which ISTA argued that its once-a-day formula (Bromday®) for bromfenac ophthalmic solution was safer than its withdrawn twice-a-day formula (Xibrom®), and thus any ANDA referencing Xibrom must be denied. FDA concluded, "[e]ven if Bromday were shown to be safer than Xibrom, that would not necessarily mean that Xibrom should no longer be considered sufficiently safe. Rather, the Agency would evaluate Xibrom's risks in light of its benefits, including any evidence that showed Xibrom offers any material efficacy advantage over Bromday."[50] Both a first-generation and a second-generation can be safe. In a similar situation, FDA determined that the approval of a potentially safer second generation drug did not equate to a decision that the first generation drug was unsafe. In so doing, FDA noted that petitioner's claim about a different safety profile for the second generation drug (reducing certain adverse events and allergic reactions) represented a "theoretical safety concern" that did not mean that the first generation drug was withdrawn for safety, especially where alternative attributions were possible and there was no clinical data validating the cause of the adverse events.[51] Accordingly, FDA should look at the buprenorphine/naloxone tablet dosage form and evaluate that product's risks in light of its

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[48] S. Thaxter, RBP CEO, *Building a sustainable growth business*, Reckitt Benckiser Pharmaceuticals Slide Presentation, July 2012, at Slide 3, *available at* http://www.rb.com/DocumentDownload.axd?documentresourceid=29338.

[49] D. Jones, "Reckitt to discontinue Suboxone® tablets in U.S.," Reuters, Sept. 25, 2012 ("The film has taken around 60-70 percent of the Suboxone® market in the United States. The company's pharmaceutical division, which makes around 22 percent of group profits, relies on Suboxone® for the bulk of its annual sales."), *available at* http://www.reuters.com/article/2012/09/25/us-reckitt-benckiser-idUSBRE88O0GQ20120925.

[50] FDA Response to Citizen Petition, Letter to ISTA Pharmaceuticals, FDA Docket Nos. FDA-2008-P-0368 and FDA-2011-P-0128 (May 11, 2011), at 16.

[51] FDA Response to Citizen Petition, Letter to Leydig, Voit & Mayer and Covington & Burling, FDA Docket Nos. FDA-2011-P-0339 and FDA-2012-P-0507 (Nov. 7, 2012), at 5-6.

benefits. In so doing, we are confident that FDA will continue to find that the tablets are sufficiently safe and were not withdrawn from the market for safety reasons.

C. If Granted, the Petition Would Harm Numerous Parties by Excluding Cost-effective Generic Drugs from the Market, Indefinitely

If FDA grants the petition and denies the ANDAs for buprenorphine/naloxone tablets, a multitude of healthcare payors would be forced to pay higher prices for a drug that could, and should, be generically available. For example, federal and state government payors and commercial healthcare payors would be forced to pay the higher dollar values associated with RBP's film product. But buprenorphine/naloxone tablets are not the "average" drug, purchased at a pharmacy by the majority of Americans. Instead, this drug is often purchased by local governments, public assistance programs, and non-profit groups who purchase the tablets for use in addiction clinics, abuse treatment programs and halfway houses, as well as by patients who need addiction assistance via medicinal therapy. These groups, in particular, should not be limited to only one dosage form for the buprenorphine/naloxone combination, and should not be forced to pay monopoly prices for Suboxone film. This is especially so when RBP has already obtained the benefit from the market exclusivity that it was awarded for initially developing the buprenorphine franchise.

IV. Conclusion

In sum, there is no regulatory validity or scientific merit to the RBP petition's requests. For all of the foregoing reasons, FDA should summarily deny RBP's citizen petition, and continue to process the pending ANDAs for buprenorphine-containing drug products to a final approval.

Sincerely,

The BPMG
The current member companies of the BPMG include:
Actavis, Inc.
Amneal Pharmaceuticals LLC
Ethypharm USA Corp
Mylan Inc.
Roxane Laboratories Inc.
Sandoz Inc.
Sun Pharmaceuticals Industries, Ltd.
Teva Pharmaceuticals USA, Inc.